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Appellants:	John B. Hurley, Judith A. James, and Kenneth M. Kaufman		
Serial No:	09/500,904	Art Unit:	1648
Filed:	February 9, 2000	Examiner:	Foley, S.
For:	DIAGNOSTICS AND THERAPY OF EPSTEIN-BARR VIRUS IN AUTOIMMUNE DISORDERS		

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FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

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Complete if Known	
Application Number	09/500,904
Filing Date	February 9, 2000
First Named Inventor	John B. Harley
Examiner Name	S. Foley
Art Unit	1648
Attorney Docket No.	OMRF 161 CIP

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1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

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			Extra Claims		Fee from below	=	Fee Paid
Total Claims	9	-20** =	0	X	0	=	0
Independent Claims	2	-3** =	0	X	0	=	0
Multiple Dependent						=	

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

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1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	**
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
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1806	180	1806	180	Submission of Information Disclosure Stmt	
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1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

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Name (Print/Type)	Patrea L. Pabst	*Registration No. (Attorney/Agent)*	31,284	*Telephone*	(404) 817-8473
Signature				*Date*	April 5, 2004

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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission

Application Number	09/500,904
Filing Date	February 9, 2000
First Named Inventor	John B. Harley
Art Unit	1648
Examiner Name	S. Foley
Attorney Docket Number	OMRF 161 CIP

ENCLOSURES *(Check all that apply)*

- [x] Fee Transmittal Form
- [ ] Fee Attached
- [ ] Amendment/Reply
- [ ] After Final
- [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
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- [ ] Information Disclosure Statement
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Firm or Individual name	Patrea L. Pabst, Esq., Reg. No. 31,284 Holland & Knight LLP Suite 2000, One Atlantic Center, 1201 West Peachtree Street, N.E.; Atlanta, GA 30309-3400
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants:	John B. Harley, Judith A. James, and Kenneth M. Kaufman		
Serial No:	09/500,904	Art Unit:	1648
Filed:	February 9, 2000	Examiner:	Foley, S.
For:	DIAGNOSTICS AND THERAPY OF EPSTEIN-BARR VIRUS IN AUTOIMMUNE DISORDERS		

Commissioner for Patents
Washington, D. C. 20231

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 6-10 and 19-22 in the Office Action mailed November 5, 2003, in the above-identified patent application. A Notice of Appeal (and Replacement Supplemental Information Disclosure Statement) were filed on February 5, 2004. The fee for the filing of this Appellants' Brief was submitted with the previously filed Appeal Brief on January 6, 2003. The Examiner had withdrawn finality in view of this Appeal Brief, but reinstated the same rejections in the Office Actions mailed April 23, 2003 and November 5, 2003.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is the assignees, the Oklahoma Medical Research Foundation, Oklahoma City, OK, The Board of Regents of the University of Oklahoma Health Science Center, Oklahoma City, OK, and the licensee, JK Autoimmunity, Inc., Oklahoma City, OK.

(2) RELATED APPEALS AND INTERFERENCES

The following related appeals are known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which may have a bearing on the Board's decision in this appeal:

U.S.S.N. 08/475,955 filed June 7, 1995. A copy of the decision in this application was placed in this file. The examiner questioned the relevance, but the undersigned believes that the technology is related and issues on appeal are related. U.S.S.N. 08/475,955 is drawn to the discovery of the viral peptides that elicit an autoimmune reaction in the patient, which are correlated with the development of lupus in patients previously exposed to the virus. The claims in this case are drawn to a diagnostic method which can use these peptides as antigen to measure levels of antibodies indicative of autoimmune disease in the patients exposed to the virus.

U.S.S.N. 08/781,296 filed January 13, 1997 by John B. Harley and Judith A. James entitled "Diagnostics and Therapy of Epstein-Barr Virus in Autoimmune Disorders", of which this is a continuation-in-part has been on appeal. The examiner changed and prosecution was reopened. It is possible the case will be back on appeal since the most recent office action reiterated the rejections on appeal.

(3) STATUS OF CLAIMS ON APPEAL

Claims 6-10 and 19-22 are pending and on appeal. The text of each claim on appeal, as amended, is set forth in the Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

The pending claims were last amended by the Amendment mailed July 23, 2003.

(5) SUMMARY OF THE INVENTION

Differences have been identified in the immune responses to Epstein-Barr infection between individuals who develop a specific autoimmune disease and those who do not. (page 8, lines 20-22). These differences are used in the claimed diagnostic assay kits and methods of use thereof to distinguish those who are at greater risk for developing specific autoimmune diseases from those who are a lesser risk. (page 8, lines 22-24) Individuals who are not at as great a risk for developing autoimmune disease can be identified by reactivity to various peptides, for example, as demonstrated in the examples where individuals who are not prone to develop lupus are characterized by antibodies to GAGAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO: 7). (page 2, lines 15-19) Subsets of antigenic peptides can be used to identify patients at risk for particular clinical manifestations or patients in particular prognostic groups. (page 26, lines 21-23) The peptides can be used in combination in assays, such as the solid phase assay, to classify patients. (page 26, lines 23-24)

(6) ISSUES ON APPEAL

The issues presented on appeal are

(1) whether claims 6-10 and 19-22 are enabled under 35 U.S.C. 112, first paragraph.

(2) whether claims 6-10 and 19-22 are obvious under 35 U.S.C. 103 over Petersen, et al. Arthritis and Rheumatism 33(7):993-1000 (1990).

(3) whether claims 6-10 and 19-22 are obvious under 35 U.S.C. 103 over Marchini, et al. J. Autoimmunity 7:179-191 (1994) in combination with Petersen, et al.

Claims 6-10 and 19-22 were *provisionally* rejected under the doctrine of obviousness-type double patenting over claim 35 of U.S.S.N. 08/781,296. This rejection will be addressed either by filing of an appropriate Terminal Disclaimer or by cancellation of claim 35 in the co-

pending application, once the claims have otherwise been determined to be allowable in the two applications.

(7) GROUPING OF CLAIMS

The claims do not stand or fall together, as discussed in more detail below.

(8) ARGUMENTS

(i) The Invention

Differences have been identified in the immune responses to Epstein-Barr infection between individuals who develop a specific autoimmune disease and those who do not. These differences are used to distinguish those who are at greater risk for developing specific autoimmune diseases from those who are a lesser risk. For example, individuals who are not at as great a risk for developing autoimmune disease can be identified by reactivity to the various peptides, for example, as demonstrated in the examples where individuals who are not prone to develop lupus are characterized by antibodies to GAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO: 7). Other structures derived from Epstein-Barr virus can be used to predict who will develop autoimmune disease. These structures were identified using standard techniques, the known sequences of the Epstein-Barr viral proteins and the known sequences of the autoantigens such as Sm B' and Ro/SSA, and sera from many patients, including a large data base that spanned a number of years in the same patients, allowing the appellants to follow the progression of the disease and markers for the disease, over a period of years. Comparison with normals or individuals who did not develop the disease allow those skilled in the art to identify individuals who are more likely than not to develop autoimmune disease.

The claims are drawn to the following:

Claim 6 has been amended to define a diagnostic assay or test for predicting the risk of developing lupus as including the following reagents:

(1) reagents which can be used to detect in a patient sample materials which are indicative of Epstein-Barr viral infection:

(a) levels of antibodies to Epstein-Barr virus,

(b) levels of indicators of Epstein-Barr infection of cells, or

(c) levels of Epstein-Barr DNA or protein in a patient,

wherein the reagents used to detect antibodies to peptides from Epstein-Barr virus are peptides of up to forty amino acids in length comprising an amino acid sequence selected from the group consisting of PPPGRRP (SEQ ID NO:1), GRGRGRGG (SEQ ID NO:2), RGRGREK (SEQ ID NO:3), GAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7), GPQRRGGDNHGRGRGRGRGGGRPG (SEQ ID NO:98), GGSGSGPRHRDGVRRPQKRP (SEQ ID NO:25), RPQKRPSC (SEQ ID NO:26), QKRPSCIGCKGTHGGTG (SEQ ID NO:27), GTGAGAGARGRGG (SEQ ID NO:99), SGGRGRGG (SEQ ID NO:100), RGGSGGRRGRGR (SEQ ID NO:101), RARGRGRGRGEKRPRS (SEQ ID NO:102), SSSSGSPPRRPPPGR (SEQ ID NO:103), RPPPGRRPFFHPVGEADYFEYHQEG (SEQ ID NO:104), PDVPPGAI (SEQ ID NO:33), PGAIEQGPA (SEQ ID NO:34), GPSTGPRG (SEQ ID NO:105), GQGDGGRRK (SEQ ID NO:37), DGGRRKKGGWFGKHR (SEQ ID NO:38), GKHRGQGGSN (SEQ ID NO:106), GQGGSNPK (SEQ ID NO:107), NPKFENIA (SEQ ID NO:108), RSHVERTT (SEQ ID NO:109), VFVYGGSKT (SEQ ID NO:110), GSKTSLYNL (SEQ ID NO:111), GMAPGPGP (SEQ ID NO:46), PQPGPLRE (SEQ ID NO:47), CNIRVTVC (SEQ ID NO:48), RVTVCSFDDG (SEQ ID NO:49), PPWFPPMVEG (SEQ ID NO:50) and the peptide consisting of GPQRRGGDNHGRGRGRGRGGGRPG (SEQ ID NO:98), and

(2) control samples from individuals not at risk of developing lupus, and

(3) means for determining the differences in the levels of a patient and control samples to distinguish individuals at higher risk of developing lupus from those at lower risk of developing lupus.

Claim 7 further defines the reagents of claim 6 for use in particular types of assays: assays based upon the relative presence of an antibody, assays based on cellular proliferation, assays based on molecular binding, assays based on cytokine production, assays based on skin reaction, and assays based on cell surface antigen.

Claim 8 limits the reagents to specific peptides used to detect antibodies, PPPGRRP (SEQ ID NO:1), GRGRGRGG (SEQ ID NO:2), RGRGREK (SEQ ID NO:3), GAGAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7), GPQRRGGDNHGRGRGRGRGGGRPG (SEQ ID NO:98), GGSGSGPRHRDGVRRPQKRP (SEQ ID NO:25), RPQKRPSC (SEQ ID NO:26), QKRPSCIGCKGTHGGTG (SEQ ID NO:27), GTGAGAGARGRGG (SEQ ID NO:99), SGGRGRGG (SEQ ID NO:100), RGGSGGRRGRGR (SEQ ID NO:101), RARGRGRGRGEKRPRS (SEQ ID NO:102), SSSSGSPPRRPPPGR (SEQ ID NO:103), RPPPGRRPFFHPVGEADYFEYHQEG (SEQ ID NO:104), PDVPPGAI (SEQ ID NO:33), PGAIEQGPA (SEQ ID NO:34), GPSTGPRG (SEQ ID NO:105), GQGDGGRRK (SEQ ID NO:37), DGGRRKKGGWFGKHR (SEQ ID NO:38), GKHRGQGGSN (SEQ ID NO:106), GQGGSNPK (SEQ ID NO:107), NPKFENIA (SEQ ID NO:108), RSHVERTT (SEQ ID NO:109), VFVYGGSKT (SEQ ID NO:110), GSKTSLYNL (SEQ ID NO:111), GMAPGPGP (SEQ ID NO:46), PQPGPLRE (SEQ ID NO:47), CNIRVTVC (SEQ ID NO:48), RVTVCSFDDG (SEQ ID NO:49), PPWFPPMVEG (SEQ ID NO:50).

Claim 9 limits the assay of claim 8 to a specific peptide which is predictive of an individual not developing lupus, GAGAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7).

Claim 10 defines the assay as useful for testing patients identified with or at risk of developing systemic lupus erythematosus comprising control samples from individuals with systemic lupus erythematosus (in addition to controls who do not have lupus).

Claims 19-22 define methods paralleling the limitations of the diagnostic assay of claims 6-10.

Claim 19 defines a method for determining the likelihood that an individual has lupus induced by Epstein-Barr virus, or is at risk for developing lupus, including the steps of:

(1) obtaining a sample from the individual to be tested,

(2) mixing the sample with reagents which can be used to detect levels of

(a) antibodies to Epstein-Barr virus,

(b) indicators of Epstein-Barr infection of cells, or

(c) levels of Epstein-Barr DNA or protein in a patient,

(3) analyzing the sample, and

(4) comparing the analysis of the sample with results obtained with control samples from individuals not at risk of developing lupus to determine if the differences in levels of the individual and control samples indicates the individual is at a higher risk of developing lupus than controls who are at lower risk of developing lupus.

Claim 20 parallels claim 7. Claims 21 and 22 define the same peptides as claims 8 and 9.

The methods defined by these claims are fully supported by several actual working examples in the specification, showing that the claimed method is predictive of the likelihood one will or will not develop an autoimmune disease such as lupus.

Example 1 is a study to determine which of 233 overlapping octapeptides in an autoantigen, Sm B', are indicative of disease. As shown by Figure 2, all of the anti-Sm sera (i.e., from patients with lupus) tested bound almost the identical octapeptide structures. As demonstrated by the data in the example, anti-Sm sera binds to PPPGMRPP and structurally similar sequences (Figure 3 SEQ ID NO:4). These sequences included PPPGRRP (SEQ ID NO:1), which is found in the Epstein-Barr Nuclear Antigen-1 (EBNA-1) protein. GRGRGRGG (SEQ ID NO:2) and RGRGREK (SEQ ID NO:3) are also sequences from Epstein-Barr virus Nuclear Antigen-1, but these are similar to a major antigenic epitope of Sm D in lupus patients, GRGRGRGRGRGRGRGRGRGGPRRR (SEQ ID NO:9). All three peptides bind at least three times more antibody from the anti-Sm precipitin positive lupus patient sera than the controls. The antibody binding to these peptides in the lupus patient sera was over half of the antibody binding level found for PPPGMRPP (SEQ ID NO:4).

Data was also obtained using a collection of about 80,000 specimens from 26,000 individuals collected and stored over a period of 17 years. This Clinical Immunology database was screened to identify lupus patients who developed anti-Sm under observation. The clinical serum bank was found to contain stored serum specimens from 161 patients with anti-Sm antibodies in at least one serum sample. Four patients were identified among these who, during their SLE clinical course or after initial presentation, converted from being precipitin negative to precipitin positive for antibodies to Sm. Sera from each individual were retrieved from before and after the development of anti-Sm antibodies. For each serum sample, antibody levels were tested by ELISA for binding to Sm and the Sm/nRNP complex. The Ro protein was selected as a control antigen since none of the four patients demonstrated anti-Ro antibodies by Ouchterlony immunodiffusion. Each patient increased binding towards the Sm and Sm/nRNP antigens over

time, without an increase in binding to the Ro protein (above background levels) by ELISA. Anti Sm B/B' indicated specificity was confirmed by Western blotting. Binding to Sm B/B' indicated acquisition of a new antibody specificity, since binding to this protein was not detected in the first available sample tested from each patient. Each available serum sample was tested for antibody binding to the 233 overlapping octapeptides of Sm B/B'. Each patient had antibodies which initially targeted the proline rich, repeated motif, PPPGMRP(G)P (SEQ ID NO:4). With time the response diversified to other regions of Sm B/B' when additional serum samples were available.

Sm positive patients from whom a serum sample was available from presentation were also screened. Serum samples from lupus patients stored early in the course of the disease process bind only PPPGMRPP (SEQ ID NO:4) (and neighboring peptides) of the 233 possible octapeptides of B/B', as shown by Figure 4 for one such patient. In addition to the patient presented in Figure 4, two others who initially had a simplified pattern of octapeptide binding were identified. In all three of these cases, only PPPGMRPP (SEQ ID NO:4) and PPPGMRGP (SEQ ID NO:8) were bound and no other octapeptide were bound. All other anti-Sm positive sera tested bind these octapeptides as well as others. These results are consistent with PPPGMRPP (SEQ ID NO:4) and PPPGMRGP (SEQ ID NO:8) being the first epitopes of the Sm B/B' autoantigen (Arbuckle, M. R., et al., Scan. J. Immunol. 50:447-55, 1999). This repeated PPPGMRPP (SEQ ID NO:4) motif is an early target in three additional patients tested from whom sera were available from early in their disease. In all of these patients PPPGMRPP (SEQ ID NO:4) is the first autoimmune epitope of the Sm B/B' autoantigen against which one can detect antibody binding.

Four peptide sequences from Epstein-Barr virus were separately evaluated for binding to sera from patients with an autoimmune disease (Figures 3 and 7). All are found in the EBNA-1 (Epstein-Barr virus Nuclear Antigen-1) protein. Subjects with an autoimmune disease, systemic lupus erythematosus, have higher levels of antibodies against PPPGRRP (SEQ ID NO:1), GRGRGRGG (SEQ ID NO:2) and RGRGREK (SEQ ID NO:3) than do normal controls. On the other hand the glycine-alanine repeat sequence, GAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7), which, after infection by Epstein-Barr virus, is a major epitope in infectious mononucleosis and in normals (Rhodes, G. et al. J. Exp. Med. 165:1026-1040 (1987)) tends not to be bound by patients with lupus (Figure 7). Figure 7 is a graph of the binding to the peptide GAGAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7) from Epstein-Barr virus Nuclear Antigen-1 by lupus sera who all had anti-Sm and anti-nRNP precipitins, as compared to normal control sera. The structures (octapeptides from Epstein-Bar virus nuclear antigen-1) bound by the lupus sera tested is listed in Table 8. These are taken from epitopes with average binding greater than 3 standard deviations about the normal mean (of EBV positive normal controls) and commonly bound by patient sera with an O.D. greater than 0.45 absorbence units. Sequences longer than eight amino acids represent neighboring octapeptides that exceed the 0.450 A U.

Other sequences have also been identified. As described by Example 10, PPPGMRPP (SEQ ID NO:4) constructed on a multiple antigenic peptide (MAP) backbone was coupled to CNBr activated Sepharose™. Each MAP molecule contains eight copies of the PPPGMRPP (SEQ ID NO:4) peptide on a branching polylysine backbone. One ml of sera from a Sm precipitin positive black female lupus patient was passed over the column and extensively washed. Bound antibodies were removed with 3 M guanidine and then dialyzed against 25 mM Tris-HCl pH 8.0. The column affinity purification was repeated using the first round bound

material. Purified antibodies were concentrated and quantitated by UV absorption. In order to identify the peptide epitopes recognized by human anti-PPPGMRPP (SEQ ID NO:4) antibodies, a random heptapeptide phage display library from New England Biolabs (Bar Harbor, MA) was screened. A heptapeptide library was selected because all 1.28×10^9 seven amino acid possibilities could be represented (8 a.a.= 2.56×10^{10} combinations, 9 a.a. = 5.12×10^{11} combinations). In this library each random heptapeptide is expressed at the N-terminus of the pIII minor phage coat protein followed by a Gly-Gly-Gly spacer. There is on average five copies of the pIII protein per phage particle. Theoretically, every combination of seven amino acid sequences could be expressed. Antibody-phage complexes were isolated by incubation with protein-A agarose. Following the fourth round of amplification, 70 clones were isolated and sequenced (Table 9). Eleven distinct sequence motifs were identified. Both class I and class II motifs share obvious homology to PPPGMRPP (SEQ ID NO:4) peptide. The binding of anti-PPPGMRPP (SEQ ID NO:4) antibodies to the different types of peptides displayed on the phage was then characterized. Figures 8A-E are graphs of the binding to the overlapping octapeptides from Epstein-Barr virus Nuclear Antigen-1. The binding of three controls are presented in Figures 8A, 8B and 8C and that of two lupus sera in Figures 8D and 8E. Figure 8A is from a normal who has no evidence of having been infected by Epstein-Barr virus by the assay for anti-Epstein-Barr virus Viral Capsid Antigen IgG. The other sera presented (Figures 8B through 8E) are all positive in this assay. The peptides presented had average reactivity at least 3 standard deviations above the normal mean. Sequences longer than eight amino acids represent neighboring octapeptides that exceed the 0.450 A.U. threshold.

Example 9 demonstrates that one can screen for the antibodies using cell line lysates rather than the peptides. Three different cell lines: B95 (marmoset cell line with the most

common strain, EBV-1 or –A), Jiyoye cell line (from Burkitt's lymphoma with EBV-2 or –B), and the Ramos cell line which has no EBV infection were obtained. 15 patient and 13 control sera were screened for binding to these different cells lysates. Anti-EBNA-1 is quite obvious as an approximate 70 kD band. All 15 patient sera, as well as 11 of 13 control sera, strongly bind the EBNA-1 protein in both strains. An EBNA-1 monoclonal antibody confirms the identify of this band. Many other proteins are bound by patient and control sera, however there appears to be more patient sera binding to approximately 90 kD, 58 kD, 50 kD, and 36 kD bands.

In summary, the claims define a diagnostic kit and method of use for determining the likelihood that an individual will develop an autoimmune disease. As the examples demonstrate, these assays, and reagents for use therein, have been made, tested, and demonstrated to yield statistically significant results. The examples clearly *establish a statistically significant correlation between EBV and lupus. There is no other legal requirement.*

(ii) Rejection Under 35 U.S.C. § 112, enablement

(a) The legal requirements under 35 U.S.C. 101 and 112, first paragraph

An invention must have utility. This requirement can be found in U.S.C. § 101 which states," Whoever invents or discovers any new and *useful* process or . . . composition of matter . . . may obtain a patent . . ." (emphasis added). This requirement is also implicitly found in 35 U.S.C. § 112 which requires the specification to provide a written description for "making and *using*" the claimed subject matter.

Whether the utility requirement comes from 35 U.S.C. § 101 or 35 U.S.C. § 112, the standard to be applied is the same. *Ex parte Maas*, 14 USPQ2d 1762, 9 USPQ2d 1746, 1747 (Bd. Pat. App. & Int'f 1987). The *Maas* court stated, "the issue under 35 U.S.C. § 112 relating to an enabling disclosure is subsumed within the issue under 35 U.S.C. § 101 relating to patentable

utility." Any analysis of a claim under 35 U.S.C. § 112, first paragraph relating to the use of the claimed subject matter, need only meet the standards of the utility requirement of 35 U.S.C. § 101 because if the claimed subject matter meets the utility requirement it is presumed to meet the enablement requirement of use.

To meet the utility requirement the invention must simply have a "practical utility" in the "real world sense." (*Nelson v. Bowler*, 626 F.2d 853, 856 (CCPA, 1980)). Any use which gives immediate benefit to the public is sufficient to be a "practical utility". *Id.* at 856. It is clear that for an invention to have "practical utility" it must be operative. However, to fail the utility requirement the claimed subject matter must be "totally incapable of achieving a useful result. ("In short, the defense of non-utility cannot be sustained without proof of total incapacity.").) (*Brooktree Corp v. Advanced Micro Devices. Inc.*, 977 F.2d 1555 (Fed. Cir. 1992). See also *E.I. du Pont De Nemours and Co. v. Berkley and Co.*, 620 F.2d 1247, 1260 n.17, 205 USPQ 1, 10 n.17 (8th Cir. 1980). An assertion of utility is sufficient to meet the utility requirement unless the assertion is "incredible in the light of the art or factually misleading." (*In re Citron*, 325 F.2d 1389 (CCPA, 1963)).

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*See, e.g.*, Genentech, Inc. v. Novo Nordisk A/S, 108 F3d at 165, 42 USPQ2d at 1004 (quoting In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also In re Fisher, 427 F.2d at 839, 166 USPQ at 24; United States v. Telectronics, Inc., 857 F.2d 778 (Fed. Cir. 1988); In re Stephens, 529 F.2d 1343 (CCPA 1976)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (M.I.T. v. A.B. Fortia, 774 F.2d 1104 (Fed. Cir. 1985)). In addition, as

affirmed by the Court in Spectra-Physics, Inc. v. Coherent, Inc., 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether making or using the invention would have required undue experimentation, and thus whether the disclosure is enabling, is a legal conclusion based upon several underlying factual inquiries. See In re Wands, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988). As set forth in Wands, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' Atlas Powder Co., v. E.I. DuPont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).

> The test is not merely quantitative, since a considerable amount of experiment is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.
>
> Ex parte Jackson, 217 USPQ 804, 807 (1982)

As stated in the MANUAL OF PATENT EXAMINING PROCEDURE §2164.04 (7th ed. 1998), *citing* In re Wright, 999 F.2d 1557, 1562 (Fed. Cir. 1993), the examiner has the initial burden to establish a reasonable basis to question the enablement of the application.

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must be taken as being in compliance with the enablement requirement** of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.
>
> *Id.* at § 2164.05 (emphasis added).

(b) The claims comply with 35 U.S.C. 112, first paragraph

The Examiner's argument in support of the rejection begins with an incorrect premise: "the specification, while being enabling for detecting the presence of EBV, does not reasonably provide enablement for predicting the risk of developing lupus by detecting the presence of EBV." (last line page 3 - top of page 4, office action mailed November 5, 2003).

Appellants are not detecting the presence of EBV.

Appellants are detecting the presence of antibodies to very specific antigens found within certain EBV proteins.

The data in the application show that individuals who have never been infected with EBV do not have antibodies to any of the EBV antigens - neither those that are predictive of developing lupus nor those that are predictive of not developing lupus. This is what one skilled in the art would expect.

However, the data in the application also demonstrates that ***following infection, indeed, long after the viral infection has disappeared***, individuals develop antibodies to different viral epitopes. It is the specificity of these antibodies that determines the likelihood the individual will develop lupus, and indicate if the individual has already developed lupus.

In a totally unexpected finding, possible because appellants had access to thousands of samples collected over decades, including samples collected over extensive periods of time for the ***same individuals***, appellants demonstrated that antibodies that arose due to the initial viral infection expand in their specificity to encompass epitopes that were not reactive with the initial antibodies. When these epitopes are also present in "self" proteins, the antibodies elicited by the original viral infection become "autoantibodies", i.e., antibodies against "self", causing lupus, a devastating autoimmune disease.

The examiner's arguments on page 5 of the office action rely on the fact that the prior art does not disclose that which is claimed! Of course the prior art does not disclose what is claimed: the prior art did not have access to the samples that appellants were able to test and analyze, nor did the prior art recognize "epitope spreading", a phenomena only very recently understood, primarily based on appellants' work.

There is no legal requirement that the prior art support the claimed method - indeed, what makes the claimed method and reagents patentable is that they are neither disclosed by, nor obvious from, the prior art, as discussed in more detail below.

The examiner's position is similar to that encountered by the researcher who discovered that many stomach ulcers are caused by a little known bacteria called *Helicobacter pylori* - all the prior art said stomach ulcers were caused by stress, not bacteria. Now the first line of

treatment for stomach ulcers is antibiotics. Just because the prior art does not support the appellants' position does not mean it lacks enablement.

The examiner's focus on the alleged lack of appropriate controls is simply wrong. Appellants state that one can use as controls individuals who do not develop lupus. Although these are individuals who do not have antibodies with the claimed reactivity, they are also readily identified by those skilled in the art as not having the characteristics defined by the American College of Rheumatologists for lupus patients.

Appellants have met the legal requirements. As discussed above, the application contains a number of examples that show that one can differentiate between samples of patients with lupus and controls that do not have lupus, both prior to development of symptoms as well as after development of symptoms. These examples demonstrate that specific peptide sequences have been obtained which can be used to screen sera from patients for antibodies which bind to the peptides, some of which are indicative of disease (to a degree that there is 300% more binding from those with or developing disease as compared to negative controls) and some of which are indicative that a patient will not develop disease (the peptide of claims 9 and 22). The examples also demonstrate that assays using cell lysates in functional assays (as defined by claims 7 and 20) can show differences between the two groups, as well as assays for Eppstein-Barr DNA. These examples are not hypothetical. They are based on actual patient samples. There are two groups of patients - those being tested after they have developed the symptoms of the disease and those for whom samples are available both before and after development of symptoms. The assay has been shown to be predictive with these samples as well - demonstrating that appellants had in their possession no later than the date of filing of this application, the claimed diagnostic assay and method of use thereof, that they had described the assay and method of use thereof in

sufficient detail to enable anyone of skill in the art to make and use the claimed assay and method, and that the method had utility.

The test for enablement, whether one skilled in the art could practice the claimed method, and make and use the claimed reagents, without undue experimentation, based on the specification, has clearly been met.

The test contains reagents such as antibodies to EBV antibodies, EBV proteins, or proteins which are known indicators of EBV infection; control samples which are used to eliminate "background" reactions with the reagents not indicative of developing lupus; and means for distinguishing the background reactions (i.e., the reactions between the reagents and the control samples) and the patient samples. If the reaction is greater with the patient sample than with the controls, the patient is at risk. The means are standard - in some cases, the means may be an ELISA assay, where a colored reaction is titered to quantitate the number of reactants; it may be a chromatographic assay where a spectrophotometer is used to measure the intensity of the reaction; it may be an immunoprecipitation assay. This is certainly a relative analysis, but one commonly practiced by those skilled in the art. Who has not had a blood analysis in which each determination is followed by the normal range, so that one can determine whether one is within the normal range or outside the normal range, and therefore at a great risk?

Claims 6-10 and 19-22 use the terms "likelihood" and "at risk". The terms are well known to those skilled in the art. Particularly in a case such as lupus, where there is a genetic component (same as in some types of cancer or heart disease), there are tests that can be performed to indicate if an individual is more likely than the average individual to develop a disorder, in this case, lupus. There is no legal requirement that one must establish a cause-and-effect between EBV and lupus before one can claim an assay, this is not the legal standard. The

requirement for enablement is whether or not one can make and use that which is claimed. The only essential outcome is whether or not the patient has, or is more likely than not to, develop lupus - which is all many physicians require before initiating far more expensive and comprehensive testing which would be more definitive.

In addition to the evidence in the specification, three abstracts have been submitted which provide evidence that EBV infection is at a minimum correlated with lupus:

Verdolini, et al., Br. J. Dermatol. 146(5):877-881(2002)

Dror, et al. Am. J. Kidney Dis. 32(5):825-828 (1998)

James, et al., Arthritis Rheum. 44(5):1122-1126 (2001)

No more is required under 35 U.S.C. 112, first paragraph. There is no legal requirement to "conclusively" correlate evidence that EBV cause autoimmune disease - the claims are drawn only to an assay and method of predicting the likelihood that a patient will develop the disease. This appellants have shown, using samples obtained from patients and negative controls prior to and after development of disease. Moreover, appellants have described these assays in sufficient detail to enable one skilled in the art, without undue experimentation, to practice the same assays, using the same reagents as claimed. The examiner has provided no evidence to the contrary. All that has been cited in support of the rejection is that the prior art does not establish that the claimed assay and method is useful. This, of course, is not the test under 35 U.S.C. 112.

In summary, claims 6-10 and 19-22 meet the requirements under 35 U.S.C. 112, first paragraph.

(iii) Rejections under 35 U.S.C. 103

Claims 6-10 and 19-22 were rejected under 35 U.S.C. 103 as obvious over Petersen, et al., , Arthritis and Rheumatism 33(7):993-1000 (1990) or the combination of Marchini, et al. J. Autoimmunity 7:179-191 (1994) and Petersen, et al.

a. *Marchini, et al.*

Marchini, et al. does not teach that one can predict the likelihood of developing lupus based on an EBV infection. As the examiner has correctly noted, Marchini looks at antibodies in lupus patients and determines whether or not they are reactive with EBV and SmD, an autoantigen.

b. *Petersen, et al.*

Petersen also does not teach that EBV viral infection is predictive of the likelihood of developing lupus. Petersen, et al. only looks at samples ***after infection and development of autoimmune disease***, same as Marchini. As the examiner correctly notes, Petersen does not teach the claimed peptides, *much less that some are used to indicate the likelihood some will develop lupus and some will not.* Only with experimental data and extensive statistical analysis can one determine that there is a correlation between EBV infection and whether someone develops lupus. The examiner has recognized this as well.

With respect to the sequences that the examiner has cited, which is relevant only to the assay claims, these are different from the claimed sequences. The examiner, on page 9 of the office action, states that Petersen, et al., teaches the amino acid sequence of EBNA-1. However, appellants are not claiming the amino acid sequence of EBNA-1. To the extent that appellants are claiming peptides, these are very specific sequences within the protein. The claimed peptides are limited to the specified sequences, or peptides of no more than forty amino acids containing

these sequences. The examiner has pointed out where there is overlap, and where certain sequences fall within a much longer peptide. This is not enough.

To make the claimed peptides obvious, the prior art must disclose the specific sequence and a teaching that would lead one to select the claimed sequence. To make obvious a diagnostic kit, or method of use thereof, the prior art must go further, and teach one that the peptide would be useful in determining whether or not an individual would be predictive of a patient having or developing lupus.

None of the prior art does this. There is absolutely nothing in Marchini or Petersen that leads one to the claimed peptides, nor to have a reasonable expectation of success. "the clear difference in epitope specificity in each group of patients", where the difference in the groups is rheumatoid arthritis and convalescent mononucleosis patients, does not lead to who is expected to develop autoimmune disease - the second group may in fact ultimately overlap with the first group! The invention is to understand that one can correlate the likelihood of disease, or development of disease, with reactivity with ***specific peptides***, not just any EBV peptides.

Therefore, the prior art fails to teach the claimed elements, how to modify the sequences to arrive at those claimed by applicants, or any reasonable expectation of success.

Indeed, Petersen, et al. teaches away from the claimed method because Petersen only looks at patients ***after*** they have developed the autoimmune disease; applicants claims require testing ***prior*** *to development of the autoimmune disease - indeed, what would the point be after the disease has occurred - one clearly knows at that point that the patient is going to develop autoimmune disease.*

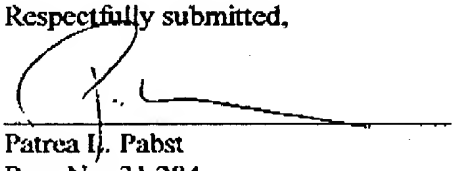
There is nothing to lead one of ordinary skill in the art to the claimed peptides. It is not enough to say someone would have motivation to look for a reagent: the prior art must lead one

skilled in the art to what is claimed, with a reasonable expectation of success. Therefore the claimed reagents cannot be obvious over Petersen.

(9) SUMMARY AND CONCLUSION

Based on the foregoing, the compositions of claims 6-10 and methods of claims 19-22 are enabled and not obvious over the prior art.

Respectfully submitted,



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